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Research Article

Optimization of the Microwave-Assisted Extraction of Total Phenolic Compounds (TPCs) From Almond Skins Through Artificial Neural Networks (ANNs) and Assessment of the Antioxidant and Antihyperglycemic Activity of the Extracts

Lila Harkat-Madouri,[1,2] Hanane Touati,[1] Lila Boulekbache-Makhlouf,[1] Khodir Madani,[1,3] and Hayate Haddadi-Guemghar[1]

[1]*Laboratoire de Biomathématiques, Biophysique, Biochimie, et Scientométrie (L3BS), Faculté des Sciences de la Nature et de la Vie, Université de Bejaia, Bejaia, Algeria*
[2]*Faculté des Sciences Biologiques, Université des Sciences et de la Technologie Houari Boumediene (USTHB), Bab Ezzouar, Algeria*
[3]*Centre National de Recherche en Technologies Agroalimentaires, Bejaia, Algeria*

Correspondence should be addressed to Hayate Haddadi-Guemghar; hayate.haddadi@univ-bejaia.dz

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Optimization by response surface methodology (RSM) and artificial neural networks (ANNs) was efficaciously applied to study the operating parameters of microwave-assisted extraction (MAE) in the recovery of total phenolic compounds (TPCs) from almond skins. These models were used to evaluate the effects of process variables and their interaction towards the attainment of their optimum conditions. A comparison of statistical parameters showed that ANN was more consistent ($R^2 = 0.99$) than RSM ($R^2 = 0.97$) to predict a TPC by MAE. Therefore, the following conditions were proposed: microwave power of 562 W, extraction time of 30 s, and ethanol concentration of 53%, corresponding to an optimal TPC yield of 560.79 mg gallic acid equivalents (GAEs)/100 g of dry weight (DW). The almond skin extract exhibited a high antioxidant activity tested by 1,1-diphenyl-picrylhydrazyl (DPPH) radical scavenging activity ($IC_{50} = 5.39 \pm 0.35\ \mu g/mL$), phosphomolybdate ammonium essay, hydroxyl radical scavenging activity (IC_{50}042002mg/mL), and ability of chelating ferrous ions. The in vitro antihyperglycemic activity test revealed that the almond skin extract inhibits strongly α-amylase activity with $IC_{50} = 27.87\ \mu g/mL$ which was close to IC_{50} of the therapeutic drug acarbose ($IC_{50} = 14.24\ \mu g/mL$).

Keywords: antidiabetic activity; antioxidants; ecoextraction; experimental design; modelization; *Prunus amygdalus*

1. Introduction

Good management and increased sustainability in the food industry depend on the effort to minimize waste generation and maximize by-product value [1]. Due to their high nutritional value as food, almonds are produced in large quantities, which results in the yearly generation of tons of waste [2]. Almond consumption has risen recently as a result of the food's high nutrient content and health advantages [3]. Almond production has increased significantly in the last few years, with a worldwide production of about 2.4 million tons in 2021 [4]. Because of this, there has been a greater production of related by-products, along with a growth in the almond market size [5]. Food applications of almonds in confectionery and bakery products, snack formulations, cereals, and marzipan require in most cases almonds without the skin. The external coating of almonds is industrially removed from the hot water blanching process, with the brown skin contributing to around 6.0%–8.4% of the seed weight [6]. Due to the high production of almond skins, industries are forced to consider ways of treating or using these residues since most of them are just incinerated or

dumped without control, causing several environmental problems, or used as animal feed [7].

Phenolic compounds are well-known for their antioxidant properties, which are largely attributed to their chemical structure. They can act as antioxidants through several mechanisms. Because of their antioxidant qualities, they are beneficial to human health and may provide defense against illnesses linked to oxidative stress [8].

Several studies have focused on the biological activities of almond skin extracts, such as antioxidant [9], antibacterial, antiviral [10], and anti-inflammatory activities [3]. Nearly 70% of the phenolic compounds in the entire almond fruit are found in the skin [5]. Numerous studies have shown that almond skin has advantageous phytochemical properties because it is rich in phenolic compounds like quercetin glycosides, kaempferol, naringenin, catechin, epicatechin, protocatechuic acid, and vanillic acid [2].

Microwave-assisted extraction (MAE) is a technique that improves extraction yield and extract quality. Furthermore, MAE decreases extraction time and solvent consumption compared to traditional extraction techniques [11]. However, the extraction of phenolic compounds from the plant matrix must be optimized to determine extraction conditions and obtain a good yield [12]. Response surface methodology (RSM) is a powerful technique for optimizing the extraction process. It is a set of statistical and mathematical techniques for establishing, enhancing, and optimizing processes in which a response of interest is influenced by several factors (independent variables) [13]. RSM provides a mathematical model that describes the chemical or biological processes in addition to defining the impacts of the independent variables [14]. However, the second-order polynomial equation cannot be used by the RSM technique to express complex and nonlinear biological interactions, which is one of the major drawbacks of the RSM technique.

Artificial neural networks (ANNs), comprising multiple interconnected layers of neurons, are highly effective and accurate tools for predicting complex parameters [15]. By mimicking the way the human brain processes information, ANNs excel in handling tasks that involve large volumes of data with high variability, where traditional approaches may fall short [16]. ANNs are a practical method for dealing with nonlinear relationships [17]. The advantages of employing ANNs instead of linear statistical models have been highlighted by numerous publications [17–19].

There are currently no studies comparing the optimization of MAE of almond skin polyphenolic compounds using RSM and ANNs. For this reason, the aim of this study is to use both statistical methods to optimize the conditions for extracting the MAE of total phenolic compounds (TPCs) from almond skin. The performance of RSM and ANNs was then compared using different statistical parameters. Also, the almond skin extract was investigated for its antioxidant and antihyperglycemic activities. By examining its antioxidant profile, this by-product may be used as a dietary supplement to lower oxidative stress, which has been connected to a number of chronic illnesses, including diabetes.

2. Material and Methods

2.1. Chemicals. The compounds Folin–Ciocalteu phenol reagent, 1,1-diphenyl-picrylhydrazyl (DPPH), sodium carbonate, gallic acid, sulfuric acid, sodium phosphate, ammonium molybdate, porcine pancreatic α-amylase, trolox (6-hydroxy-2, 5, 7, 8-tetramethylchroman-2-carboxylic acid), ferrous chloride, and ferrozine were purchased from Sigma–Aldrich (Taufkirchen, Germany). All solvents used were of analytical grade and purchased from Prolabo (Paris, France).

2.2. Extraction Procedure. A microwave oven (ER-SGS34 MY, Toshiba, Malaysia) measuring $519 \times 406 \times 314$ mm in W, D, and H was utilized. The device had a computerized control system with linear adjustments for both microwave power and irradiation time. To provide a consistent sample volume, the oven was adjusted to allow the vapors produced during extraction to condense into the sample. For the extraction, 1 g of the sample was placed in a round-bottom flask with 30 mL of solvent (the nature of the solvent will be specified in the preliminary study shown in Table S1 after testing three solvents; then, its concentration will be optimized). The flask was placed in a microwave oven and connected to a condenser. Then, the extract was filtered through a Whatman No. 1 filter paper. The supernatant was collected in a volumetric flask, and the extract was stored at 4°C until further use.

2.3. Determination of TPC Content. TPC content was determined by the Folin–Ciocalteu method reported by Ouatmani et al. [20]. One milliliter of Folin–Ciocalteu reagent (diluted 10 times) was mixed with 200 μL of the extract. After 5 min, 1 mL of aqueous solution of sodium carbonate (6%, (w/v)) was added. The mixture was kept for 30 min at room temperature. Absorbance was measured at 750 nm using an ultraviolet–visible (UV–Vis) spectrophotometer (model UV1800 from Shimadzu, Japan). The absorbance of the extract was compared with a gallic acid standard curve $y = 5.8386x - 0.0134$ (linearity range: 20–100 μg/mL, $R^2 > 0.999$) for estimating the concentration of TPC in the sample. The TPC was expressed as mg of gallic acid equivalents (GAEs) per 100 g of powder on a dry weight (DW) basis.

2.4. Determination of Antioxidant Activity (AA)

2.4.1. Determination of DPPH Radical Scavenging Activity. The ability of almond skin extract to scavenge stable free radicals was estimated by the DPPH method, according to the procedure described by Haddadi-Guemghar et al. [12]. An aliquot of 0.5 mL of the almond skin extract or Trolox solution (at concentrations ranging from 2 to 10 μg/mL) was mixed with 1.5 mL of an ethanolic solution of DPPH (0.2 mM). The reaction mixture was incubated for 30 min in the dark at room temperature. The absorbance of the resulting solution was measured at 515 nm using a UV–Vis spectrophotometer. Ethanol, instead of the sample solution, was used as a control. The AA of the tested samples was measured as a decrease in absorbance and was calculated using Equation (1).

$$\text{AA}\,(\%) = \frac{Ac - As}{Ac} \times 100 \quad (1)$$

where A_c and A_s are the absorbance at 515 nm of the control and sample, respectively.

2.4.2. Determination of Total AA. The total AA of the samples was evaluated by the method reported by Sethiya, Trivedi, and Mishra [21], with some modifications. A volume of 200 μL of the almond skin extract or Trolox solution (at concentrations ranging from 0.25 to 4 μg/mL) was mixed with 2 mL of the reagent solution (0.6 M sulfuric acid, 28 mM sodium phosphate, and 4 mM ammonium molybdate). The mixture was stirred and incubated in a water bath at 90°C for 90 min. For the blank, ethanol was used instead of the sample. The absorbance of the sample was measured at 695 nm.

2.4.3. Determination of Hydroxyl Radical (OH•) Scavenging Activity. The OH• scavenging activity was determined by a Fenton-type reaction reported by Yin et al. [22]. An aliquot of 1 mL of the sample at different concentrations was mixed with a volume of 1 mL of ferrous sulfate ($FeSO_4$) (9 mM). Then, 1 mL of salicylic acid–ethanol (9 mM) and 1 mL of hydrogen peroxide (H_2O_2) (9 mM) were added, respectively. After the incubation at 37°C for 30 min, the absorbance of the mixture was measured at 510 nm. The radical scavenging capacity of HO• was calculated using Equation (2).

$$\text{Hydroxyl radical scavenging activity\%} = \frac{\left[A_0 - \left(A_i - A_j\right)\right]}{A_0} \quad (2)$$

where A_i is the absorbance of the sample and A_j is the absorbance of the control (distilled water instead of H_2O_2). A_0 is the absorbance of the blank (distilled water instead of the sample).

2.4.4. Determination of the Iron (II) (Fe^{2+})-Chelating Ability. The Fe^{2+}-chelating ability of the almond skin extract at concentrations ranging from 2 to 10 μg/mL was measured by the ferrous iron–ferrozine complex method and compared to EDTA (ethylenediaminetetraacetic acid) according to the method reported by Dorman et al. [23]. The reaction mixture containing 2 mM iron (II) chloride ($FeCl_2$) (0.05 mL) and 5 mM ferrozine (0.2 mL) and the almond skin extract or EDTA (0.8 mL) was mixed and then incubated for 10 min at 25°C. The absorbance of the reaction was recorded at 562 nm. The absorbance of the control was determined by replacing the sample with ethanol. The ability of the extract to chelate ferrous ions was calculated using Equation (3).

$$Fe^{2+}\text{-chelating ability}\,(\%) = \frac{Ac - As}{Ac} \times 100 \quad (3)$$

where A_c and A_s are the absorbances at 562 nm of the control and sample, respectively.

2.5. Determination of Antihyperglycemic Activity. To assess the antihyperglycemic activity of almond skin extract, the inhibitory potential towards α-amylase was checked in vitro and compared to the therapeutic drug acarbose using a method reported by Ouatmani et al. [24]. In test tubes, 500 μL of almond skin extract at different concentrations (5, 10, 20, 30, 40, and 50 μg/mL) were added to 500 μL of α-amylase solution (0.5 mg/mL in 0.02 M sodium phosphate buffer pH 6.9). This solution was preincubated at 25°C for 10 min, after which 500 μL of 1% starch solution in 0.02 M sodium phosphate buffer (pH 6.9) was added and then incubated at 25°C for 10 min. After adding 1000 μL of dinitrosalicylic acid (DNS) reagent, the tubes were incubated in boiling water for 5 min and cooled to room temperature. The reaction mixture was diluted with 10 mL of distilled water, and the absorbance was measured at 540 nm by the UV-Vis spectrophotometer. The control was prepared using the same procedure by replacing the extract with distilled water, while the activity of the standard was tested by replacing the extract with acarbose at different concentrations (20, 40, 60, 80, and 100 μg/mL). The α-amylase inhibitory activity was calculated as percentage inhibition using Equation (4).

$$\text{Inhibition activity}\,(\%) = \frac{A_s - A_c}{A_c} \times 100 \quad (4)$$

where A_s and A_c are the absorbance values with and without the extract, respectively.

2.6. Experimental Design and Statistical Analysis

2.6.1. RSM. A central composite design (CCD), which contains a two-level full factorial design (2f) experiments), a star design (2f experiments), and center points, was used in this study in order to MAE of TPCs from almond skin. Three factors—microwave power, extraction time, and ethanol concentration—that affect extraction yield were arranged at three levels, with six replicates at the central point (20 runs). The levels of the three variables were fixed by the preliminary study shown in Table S1. The coded variables were used instead of the real variables to normalize extraction parameters. Table 1 shows the experimental design built by John's Macintosh Project (JMP) software. The optimization model, which can describe the relation between extraction parameters (microwave power A, extraction time B, and ethanol concentration C) and the yield of TPC extraction by microwaves, was fitted to quadratic polynomial equation (Equation (5)).

$$Y = \beta_0 + \beta_1 A + \beta_2 B + \beta_3 C + \beta_{11} A^2 + \beta_{22} B^2 + \beta_{33} C^2 + \beta_{12}\text{AB} + \beta_{13} AC + \beta_{23}\text{BC} \quad (5)$$

2.6.2. ANNs. ANNs are mathematical representations of the biological nervous system's operation that were developed in the field of artificial intelligence [25]. ANNs have been shown to be an effective modeling method for complex and nonlinear problems [26]. Effectively, due to their structure and underlying principles, ANNs have many characteristics with the brain, including their capacity to learn from experience [27].

Table 1: Three-level, three-variable experimental design applied for MAE and experimentally observed values of investigated response TPC.

Microwave power (W)	Extraction time (s)	Ethanol concentration (%)	Experimental (mg GAE/100 g DW)
300	30	0	41.0
600	120	40	485.6
900	30	80	373.5
900	210	0	109.8
600	120	40	452.6
300	210	80	388.6
600	120	40	499.7
300	30	80	262.6
300	210	0	20.5
900	210	80	246.2
600	120	40	451.4
900	30	0	150.8
600	120	80	415.5
300	120	40	423.7
600	120	0	141.6
600	30	40	486.2
600	210	40	435.6
600	120	40	480.7
900	120	40	460.7
600	120	40	419.6

The response output of TPC yield was predicted using the JMP software, utilizing the same data used for RSM modeling. Two-thirds of this data set was used to train the ANNs, while the remainder of the data was employed to validate the model.

The ANN model was developed by a back-propagation learning algorithm; this learning algorithm consists of three steps: computing output values and estimating weights and biases, correcting calculation errors on return trips to the network that act in the direction of the negative gradient, and updating the weights.

For assessing the statistical significance of the created ANN models, the determination coefficient (R^2), the root mean square error (RMSE), the log-likelihood test, the mean absolute deviation (MAD), and the sum of squares error (SSE) of the function were used.

3. Results and Discussion

3.1. Optimization of MAE Procedure by RSM. In RSM, natural variables are transformed into coded variables that have been defined as dimensionless with a mean zero and the same spread or standard deviation [28]. There are many factors that affect the extraction efficiency of MAE [29]. It was necessary to investigate the extraction variables in order to determine the best combination of variables for the best extraction yield. In this study, three independent variables —microwave power, irradiation time, and solvent concentration—that affect MAE of antioxidants from almond by-products were optimized using CCD. The extraction efficiency of the microwave process was estimated by measuring the TPC yield of almond skin extract. Following the experimental design by CCD, 20 runs of the extraction, including six replicates of the center points, were conducted (Table 1). During the optimization of the process from 1 g of almond skin with 30 mL of solvent, the TPC obtained ranged from 20.5 to 499.7 mg GAE/100 g DW. This deviation in the dependent variable shows a strong influence of the independent variables on the extraction efficiency, and therefore, the optimization step becomes a necessity in an extraction process.

3.1.1. Fitting the Model. The analysis of variance (ANOVA) results for the quadratic model based on TPC are summarized in Table 2. The fitness of the model was evaluated by the lack of fit test ($p > 0.05$). Statistical analysis indicated that the proposed model was adequate, possessing no significant lack of fit ($p > 0.05$) and satisfactory values of the R^2. The adjusted coefficient (adj.R^2) of determination indicates that the model accurately represents the relationship between the chosen parameters [30]. The adj.R^2 of TPC 0.96 (Table 2) indicates that the accuracy and general availability of the polynomial models are adequate. Predicted R-squared (Pred.R^2) is a measure of how well the model predicts a response value. The adj.R^2 and Pred.R^2 should be within approximately 0.20. If they are not, there may be a problem with either the data or the model. The Pred.R^2 (0.78) is in reasonable agreement with the adj.R^2. Adequate precision measures the signal-to-noise ratio. A ratio greater than 4 is desirable; thus, a ratio of 20.24 indicates an adequate signal model. The coefficient of variation (CV) describes the extent to which the data were dispersed. In general, a small value of CV gives better reproducibility, and a high CV value indicates that variation in the mean value is high and does not satisfactorily develop an adequate response model [28]. The CV value was within the acceptable range.

3.1.2. Mathematical Model and Optimal Extraction Parameters. The quadratic model calculated for TPC yield after neglecting the statistically insignificant terms ($p > 0.05$) was

$$Y = +477.33 + 1222.27C - 32.21AB - 28.82AC - 43.70A^2 - 207.35C^2 \quad (6)$$

where Y is the TPC yield and A, B, and C are the coded values of microwave power, irradiation time, and ethanol concentration, respectively.

The significance of each coefficient was determined using the F-test and p value, and it is shown in Table 2. The corresponding variables would be more significant if the absolute F-value became greater, and the p value was smaller [31]. The p value less than 0.05 indicates that the model terms are significant. In this case, ethanol concentration (C) and its quadratic term (C^2) were the major factors affecting the extraction of TPC, followed by the interaction terms of microwave power with irradiation time (AB) and microwave power with ethanol concentration (A). It can be

Table 2: Estimated regression coefficients for the quadratic polynomial model and the analysis of variance (ANOVA) for the experimental results of TPC using a quadratic response surface model.

Source	Sum of squares	df	Mean square	*F* value	Prob > *F*	
Model	4.91e + 05	9	54,567.79	52.2	< 0.0001	Significant
A —Microwave power	4180.8	1	4180.8	4	0.0734	
B —Extraction time	1289.13	1	1289.13	1.23	0.2928	
C —Ethanol concentration	1.50e + 05	1	1.50*e* + 05	143.02	< 0.0001	
AB	9360.54	1	9360.54	8.95	0.0135	
AC	6644.16	1	6644.16	6.36	0.0303	
BC	453.76	1	453.76	0.43	0.5249	
A^2	5251.76	1	5251.76	5.02	0.0489	
B^2	1719.5	1	1719.5	1.64	0.2286	
C^2	1.18e + 05	1	1.18e + 05	113.11	< 0.0001	
Residual	10,453.05	10	1045.31			
Lack of fit	8475.73	5	1695.15	4.29	0.0681	Not significant
Pure error	1977.32	5	395.46			
Cor total	5.02e + 05	19				
R^2	0.97					
Adj R^2	0.96					
Pred R^2	0.78					
Adeq precision	20.24					
CV (%)	9.53					

seen that irradiation time (*A*) did not influence the extraction yield, but its quadratic term did.

3.1.3. Response Surface and Optimal Condition Analysis. The surface plots can be used to visualize the projected model equation. These graphs, which show the relationships between the dependent and independent variables, are theoretical three-dimensional outputs of the RSM technique [14]. A CCD with 20 experiments was employed to optimize three variables including, microwave power, irradiation time, and solvent concentration, aiming at obtaining the highest TPC yield. The effects of microwave power (*A*) and irradiation time (*B*) on the TPC of the almond skin extracts are reflected in Figure 1. The independent variables *A* and *B* had a significant effect ($p < 0.05$) on the TPC. As *A* and *B* increased, the TPC sharply increased, achieving a saturated value when the extraction was performed for 210 s at 800 W. The experimental results demonstrate that an increase in microwave power from 400 to 800 W over a period of 210 s improves TPC yield up to 35.15%. High microwave power can raise the temperature of the system and result in an increase in extraction yield until it becomes insignificant or declines. It is known that the temperature is controlled by incident microwave power that controls the amount of energy provided to the matrix, which is converted to heat energy in the dielectric material. At high temperatures, the solvent power increases because of a drop in viscosity and surface tension, facilitating the solvent to solubilize solutes and improving matrix wetting and penetration [32].

Using a quadratic model to describe the experiment, three experimental variables for maximum extraction of phenolic compounds from almond skin were optimized. Optimization using the desirability function (Figure 2) indicated that the optimal conditions for the extraction of phenolic compounds with desirability of 0.89 were 661 W as microwave power, 91 s as extraction time, and 51% as ethanol concentration, giving the highest predicted yield of TPC as 498.65 ± 50.81 mg GAE/100 g DW.

3.2. Optimization of MAE Procedure by ANNs

3.2.1. Development of the ANN Model. The right network size should be chosen carefully while using ANN modeling. The network's performance will not be satisfactory if it has a very small network size (a few neurons in the hidden layer). In contrast, if the hidden layer contains an excessive number of neurons, the training will take a very lengthy time and could be hampered by local minima or overfitting [33].

The performance of an ANN model (MLP (multilayer perceptron)) was improved by adjusting the number of neurons in the hidden layer and activation functions to best fit the training data and experimental results.

Three inputs (MAE process parameters) and one output (TPC yield) were used to generate the ANN model with one hidden layer. The hidden layer's neuron count was adjusted from one to 10, and each network was repeated five times with initial biases and weights that were chosen at random. A hidden layer with six neurons and a Gaussian activation function (Figure 3) was chosen

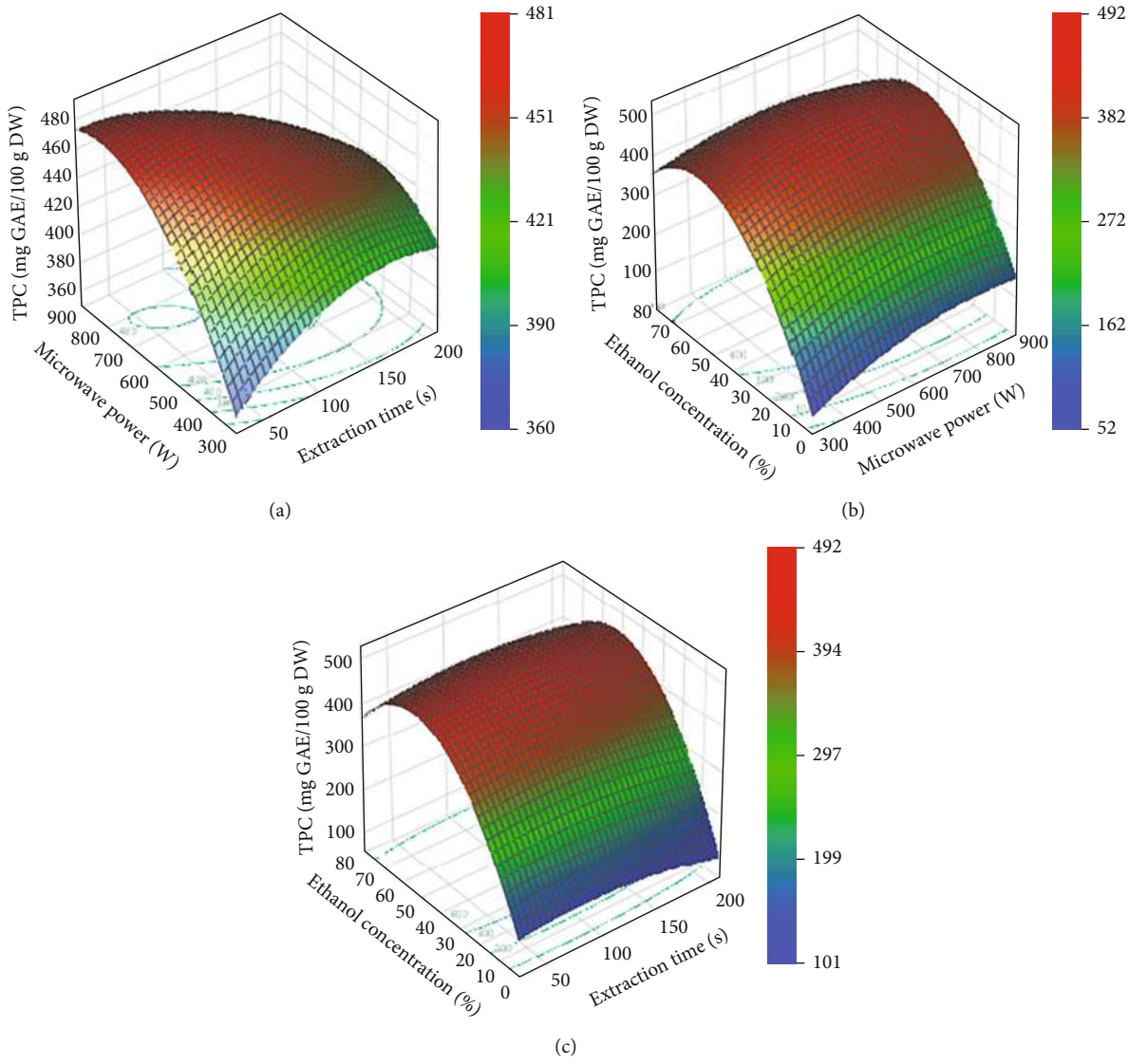

Figure 1: 3D response surface plot of TPC yields as a function of (a) microwave power (W) and extraction time (s) at ethanol concentration of 40%, (b) microwave power (W) and ethanol concentration (%) at extraction time of 120 s, and (c) extraction time (s) and ethanol concentration (%) at microwave power of 600 W, according to the RSM model.

as the best neuron network architecture, giving satisfactory statistical parameters between predicted and experimental points in both training and validation tests (Table 3).

Using the ANN model to describe the experiment, three experimental variables for maximum extraction of phenolic compounds from almond skin were optimized. Optimization using the desirability function (Figure 4) indicated that the optimal conditions for extraction of phenolic compounds with desirability of 0.99 were 562 W as microwave power, 30 s as extraction time, and 53% as ethanol concentration, giving the highest predicted yield of TPC as 560.79 mg GAE/100 g DW.

3.2.2. ANN Surface Plots. The relative impact of each extraction variable may be seen using a surface plot created in JMP by providing the ANN model with a matrix of extraction condition parameters. In order to create the surface plots, the third variable for each plot was fixed at its middle value (120 s, 40%, and 600 W), and the outcomes of this study can be seen in Figure 5. This investigation was conducted using the same methodology as with the RSM model. It is plain to see from Figure 5(a) that increasing microwave power from 300 to 900 W improves the recovery of phenolic content, which increases internal mass transfer and, in turn, increases the recovery of TPC extraction. In Figure 5(b), we can see a negative interaction effect between microwave power and irradiation time, which means that the couple microwave power and extraction time are inversely related. Figure 5(c) shows that increasing the ethanol concentration to 50% increases the extraction yields significantly to 560 mg/100 g DW. This value decreases rapidly as the ethanol concentration decreases.

3.3. Comparison Between RSM and ANN Optimization. The recovery of TPC as predicted by RSM and ANNs is

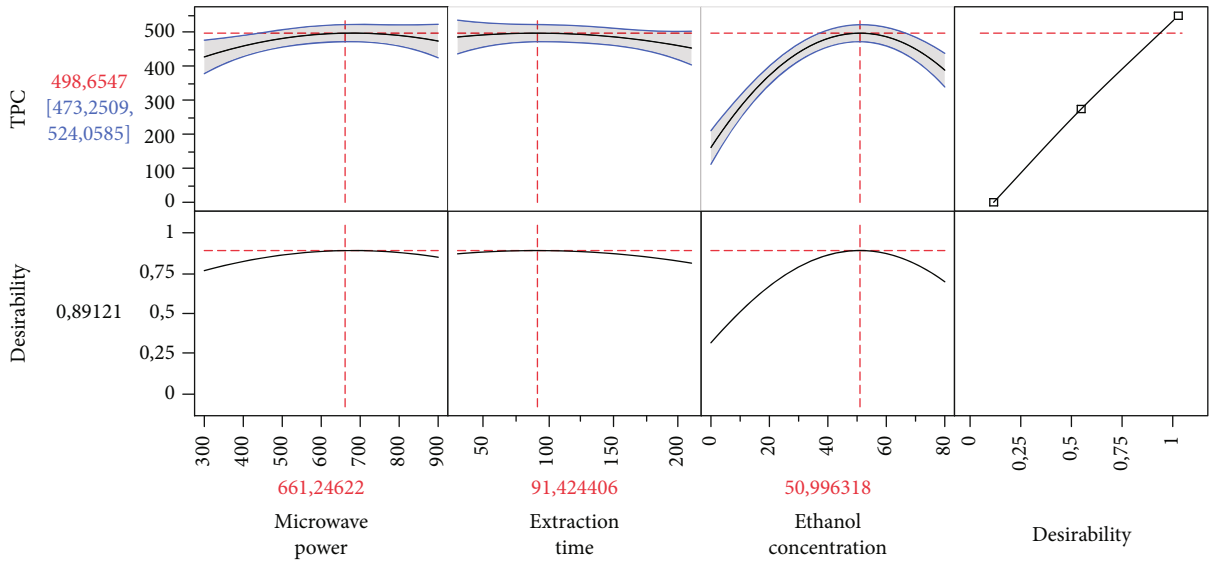

Figure 2: Profiler of prediction value and desirability function by response surface methodology.

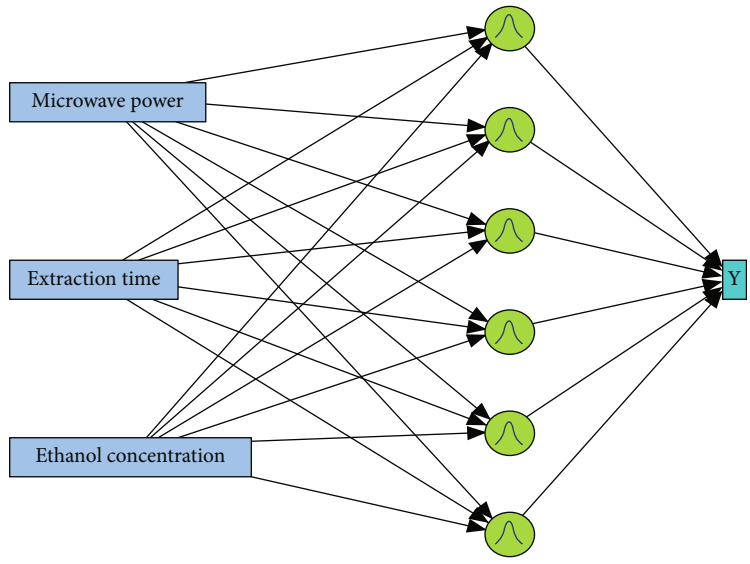

Figure 3: A schematic diagram of the neural network structure for MAE of TPC.

Table 3: The effectiveness of the ANN training and ANN validation models.

Statistical parameters	Training	Validation
R^2	0.99	0.98
RMSE	10.11	21.46
MAD	7.40	19.30
Log-likelihood test	48.51	31.39
Sum of frequency	13	7

Abbreviations: MAD, mean absolute deviation; RMSE, root mean square error.

compared to the experimentally obtained value in Table 4. The residuals obtained by subtracting the predicted value from the experimental value show that the values predicted by the ANNs are closer to the experimental values. The adequacy and precision of ANNs compared to RSM to predict responses are confirmed by the regression analysis displayed in Figure 6. This correlation is quantified by the coefficient of determination R^2. The determination coefficients (R^2) in RSM and ANNs were 0.97 and 0.99, respectively. Thus, the calculated R^2 demonstrates the superior accuracy of ANNs in contrast with the traditional optimization tool (RSM).

3.4. Validation of the RSM and ANN Models. The prediction models of extraction for TPC from almond skin were validated using the optimal extraction conditions that RSM and ANN produced. The validity and sufficiency of the RSM and ANN predicted models are confirmed by Table 5, which demonstrates that the experimental values are fairly near to the predicted values.

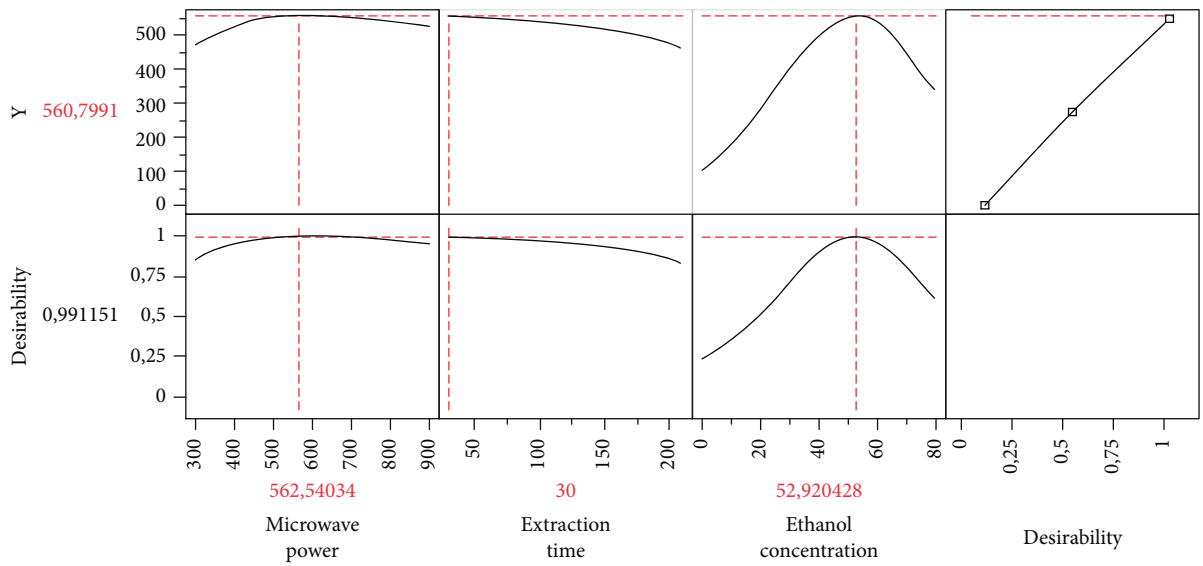

FIGURE 4: Profiler of prediction value and desirability function by the ANN model.

3.5. AA. Several studies have reported the interesting polyphenol composition of almond skins. The chemical characterization of these compounds has revealed a predominance of flavonoids, which has led to research into the biological activities of almond skins [1, 34, 35].

The AA of almond skin extract obtained at optimal extraction conditions has been assessed by DPPH radical scavenging activity, phosphomolybdate essay, hydroxyl scavenging activity, and ferrous chelation test.

The DPPH technique is widely employed for the in vitro measurement of free radical scavenging efficacy [36]. This is regarded as one of the most widely used tools to assess the free radical scavenging potential of plant extracts [37]. This method studies the ability of sample compounds to scavenge stable organic free radicals, attenuating the deep violet color that gives maximum absorbance in the 515–528 nm range. The DPPH radical-scavenging effects of almond skin extract and the Trolox hydrosoluble analog of vitamin E are presented in Figure 7(a). The results showed an increase in the scavenging activity of the almond skin extract and standard with increasing concentrations.

The DPPH radical scavenging activity results ranged from 30% to 75% for almond skin extract with an IC_{50} of $5.39 \pm 0.35\,\mu g/mL$ and 60% to 98% for Trolox with an IC_{50} of $0.71 \pm 0.02\,\mu g/mL$, which confirms that almond skin extract exhibits DPPH radical scavenging activity in a concentration-dependent manner. IC_{50} is the concentration needed to achieve a 50% antioxidant effect, which means that lower IC_{50} values indicate higher potency [38]. The obtained IC_{50} is similar to that of green tea ($6.7 \pm 0.1\,\mu g/mL$), which demonstrates strong AA when compared to other common plant extracts [39]. IC_{50} is commonly used to express antioxidant capacity and to compare the activity of various compounds. Brahmi et al. [40] reported that extracts of apple peel and grape seed decreased 50% of DPPH radical at concentrations of $97.3 \pm 4.3\,\mu g/mL$ and $12.2 \pm 0.9\,\mu g/mL$, respectively. These values are superior to those found in our study ($5.39 \pm 0.35\,\mu g/mL$). Boulekbache-Makhlouf et al. [41] reported an IC_{50} value of $2880 \pm 20\,\mu g/mL$, for eggplant extract.

By using the phosphomolybdenum method assay, the total antioxidant capacity is determined by the sample analyte's reduction of molybdenum (Mo (VI)) to Mo (V) and the subsequent creation of the green phosphate/Mo (V) complex at an acidic pH. The total AA of the almond skin extract is compared to Trolox as standard in Figure 7(b). The results showed a concentration-dependent increase in the AA of the extract in the same way as the standard.

The OH• is the neutral form of the hydroxide ion (OH-), known to be the most reactive species [42]. In this study, the effect of almond skin extract on OH• was tested and compared to that of Trolox and gallic acid. A good antifree OH• radical scavenging activity of almond skin extract as a function of the concentration is demonstrated in Figure 7(c). This activity reached 90% at a concentration of 2 mg/mL of almond skin extract. The concentration of almond skin extract needed to decrease the initial OH• radical concentration by 50% (IC_{50}) was 042002mg/mL. This value did not differ significantly ($p < 0.05$) from that of Trolox ($IC_{50} = 0.44$), which allows us to consider almond skin extract as an extract with a powerful scavenger effect on OH•.

Metal chelation is an important antioxidant property [23]. A deprotonated phenolic compound's phenoxide group has a high charge density that allows it to attach a sufficiently strongly charged cation. Rich in these components, extracts should be able to complex metal ions and maintain their shape, impeding hydroperoxide decomposition processes and metal-catalyzed initiation [43].

The potential of almond skin extract to compete with ferrozine for iron ions in a free solution was investigated and compared with that of EDTA. Almond skin extract has been shown to chelate Fe^{2+} ions in a dose-dependent manner (Figure 7(d)).

The results of this study demonstrate the ability of almond skin extract to donate electrons or hydrogens, thus

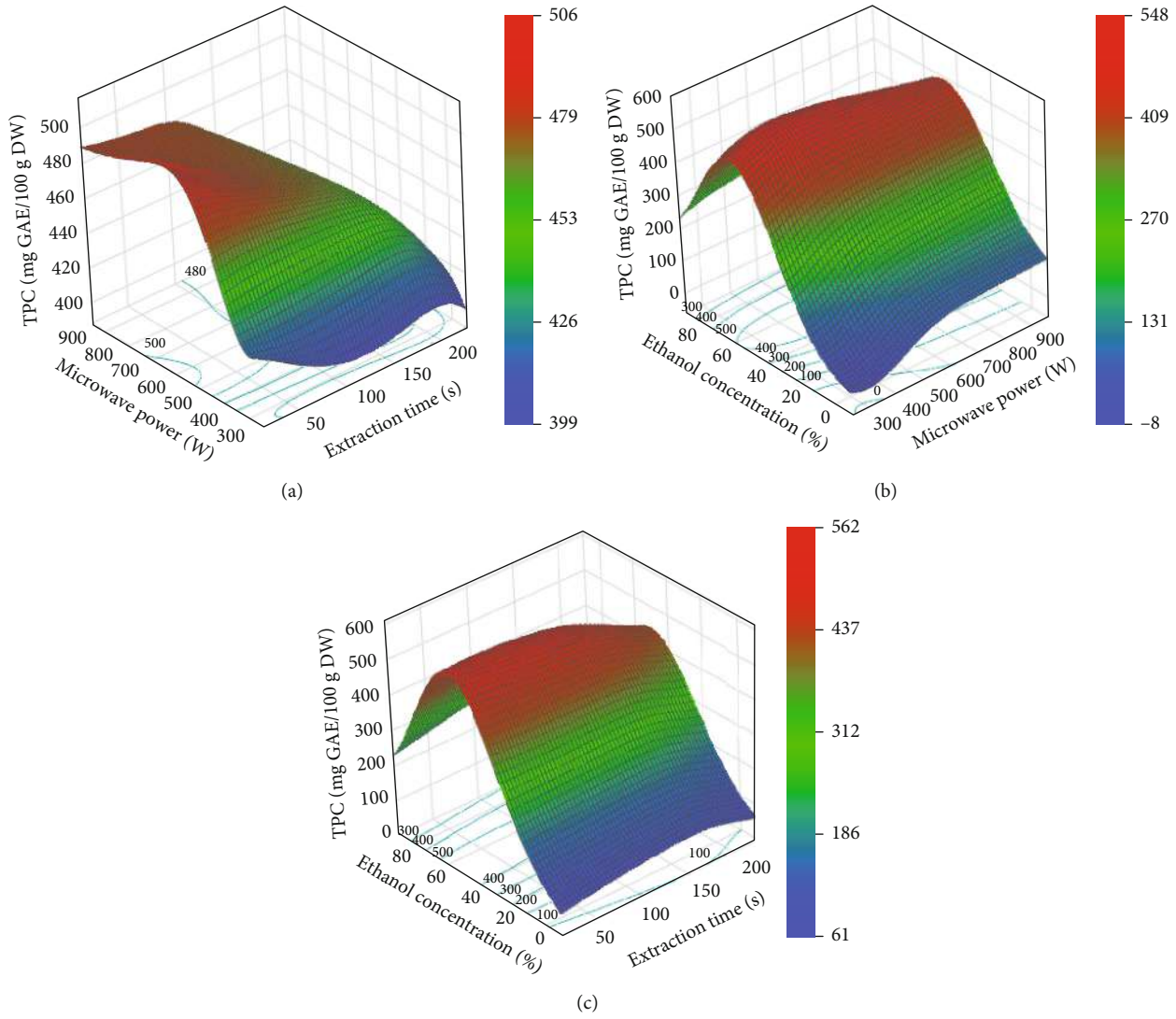

Figure 5: 3D response surface plot of TPC yields as a function of (a) microwave power (W) and extraction time (s) at ethanol concentration of 40%, (b) microwave power (W) and ethanol concentration (%) at extraction time of 120 s, and (c) extraction time (s) and ethanol concentration (%) at microwave power of 600 W, according to the ANN model.

reducing oxidants and scavenging free radicals. Additionally, it can neutralize OH• and chelate metal ions, further enhancing its AA. When compared to other natural sources of antioxidants, such as fruits, as reported in previous research, almond skin exhibits a significantly higher TPC than apple [44] and orange [45]. In fact, almond skin surpasses not only apple and orange but also the phenolic content found in pomegranate peel (168.26 mg GAE/100 g DW) [46], which is known for its antioxidant properties.

This higher TPC value in almond skin is directly linked to the greater antioxidant effect observed in this study. The phenolic compounds, including flavanols (catechin and epicatechin), flavonol glycosides (isorhamnetin-3-O-rutinoside and kaempferol-3-O-rutinoside), and phenolic acids (caffeic, ferulic, p-coumaric, and sinapic acids) which are abundant in almond skin, play a crucial role in its AA. These compounds are renowned for their ability to scavenge free radicals and chelate metal ions, which explains their protective effect against oxidative stress. Grzesik et al. [47] demonstrated that catechin and epicatechin exhibit potent scavenging activity and ferric-reducing capacity in comparison with other natural and synthetic antioxidants, attributing these effects to the presence of five hydroxyl groups in its structure, which enhance its ability to interact with free radicals and metal ions. This structural feature contributes to its strong antioxidant properties, making catechin an effective compound in neutralizing oxidative stress and protecting cells from damage [48].

3.6. Antihyperglycemic Activity. One of the therapeutic strategies for treating diabetes and reducing postprandial hyperglycemia is to delay glucose absorption through the inhibition of carbohydrate-hydrolyzing enzymes in the digestive tract [49, 50]. α-Amylase is one of the digestive enzymes; it is produced by the salivary and pancreatic glands. Salivary α-amylase first hydrolyzes 30%–40% of

Table 4: The experimental design and corresponding responses for central composite design (CCD) based on RSM and ANNs and predicted values for yield of TPC from almond skin using MAE.

Microwave power	Extraction time	Ethanol concentration	TPC yield (mg GAE/100 g DW) Experimental	Predicted ANNs	Predicted RSM	Residual ANNs	Residual RSM
300	30	0	41.04	42.86	32.64	−1.82	8.40
600	120	40	485.65	475.83	486.57	9.82	−0.92
900	30	80	373.46	369.28	371.42	4.18	2.04
900	210	0	109.78	112.29	93.40	−2.51	16.38
600	120	40	452.63	475.83	486.57	−23.20	−33.94
300	210	80	388.56	392.32	380.52	−3.76	8.04
600	120	40	499.66	475.83	449.94	23.83	49.72
300	30	80	262.65	256.86	283.12	5.79	−20.47
300	210	0	20.52	54.03	26.65	−33.51	−6.13
900	210	80	246.24	249.80	258.73	−3.56	−12.49
600	120	40	451.44	475.83	449.94	−24.39	1.50
900	30	0	150.82	152.47	162.95	−1.65	−12.13
600	120	80	415.53	389.69	392.64	25.84	22.89
300	120	40	423.73	425.83	413.57	−2.10	10.16
600	120	0	141.57	138.13	148.09	3.44	−6.52
600	30	40	486.23	499.71	464.06	−13.48	22.17
600	210	40	435.56	424.70	441.36	10.86	−5.80
600	120	40	480.71	475.83	474.72	4.88	5.99
900	120	40	460.67	477.20	454.46	−16.53	6.21
600	120	40	419.63	475.83	474.72	−56.20	−55.09

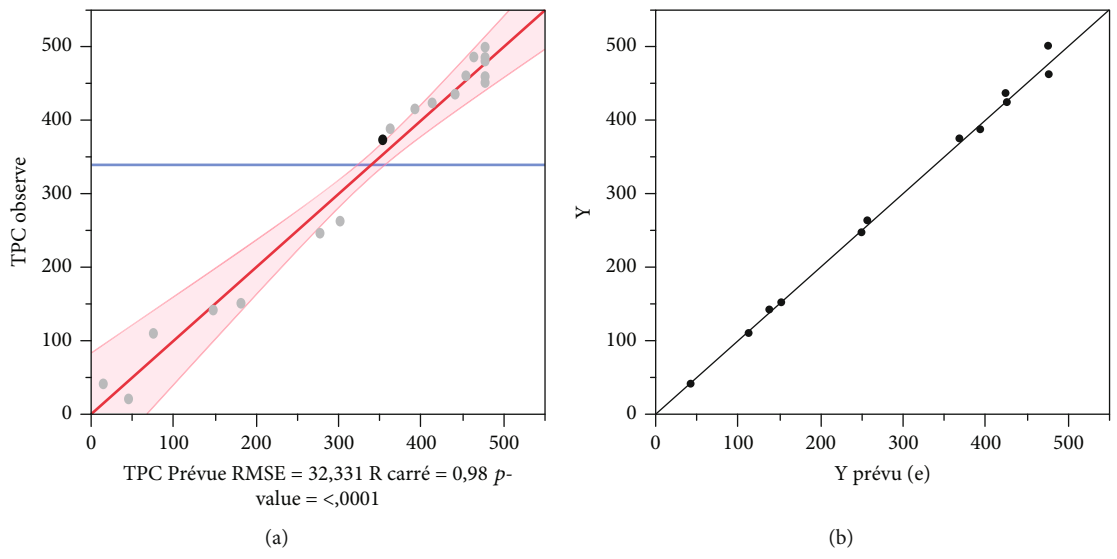

Figure 6: Comparison between experimental and predicted values of MAE content of almond skin extract TPC for (a) RSM and (b) ANN models.

ingested starch, and then, the residual starch is hydrolyzed by pancreatic α-amylase to maltose, which is converted to glucose by α-glucosidases in the small intestine [51].

Acarbose, a well-known drug, acts as an inhibitor of the α-amylase enzyme. It delays carbohydrate digestion and decreases postprandial plasma glucose levels. However, it has adverse effects such as diarrhea, hernias, and ulceration [52]. Inhibitors of α-amylase of natural origin, such as flavonoids and phenolic compounds of plants, are suggested as an alternative approach for the prevention and treatment of diabetic disease with little or no risk of side effects [53].

Table 5: Comparison of the experimental and predicted TPC values obtained under the optimized extraction conditions using the RSM and ANN models.

	Microwave power (W)	Extraction time (s)	Ethanol concentration (%)	TPC (mg GAE/100 g DW)	
				Experimental	Predicted
RSM	660	91	51	510.23 ± 21.27	498.65
ANNs	562	30	53	568.58 ± 11.23	560.79

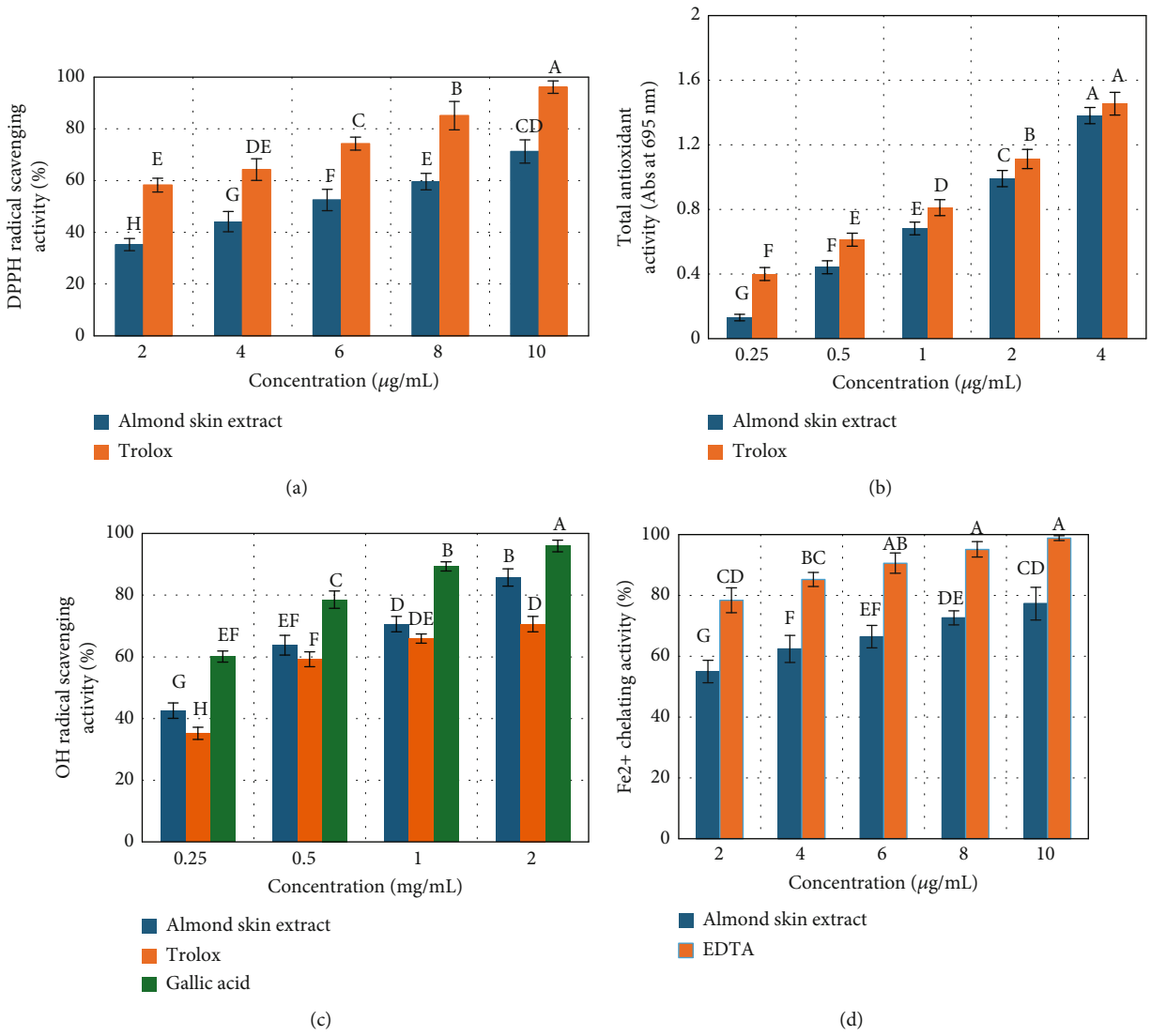

Figure 7: Antioxidant activity of almond skin extract tested by (a) DPPH scavenging activity, (b) total antioxidant activity, (c) hydroxyl radical scavenging activity, and (d) the Fe^{2+}-chelating ability. Each column and bar represent, respectively, the mean and standard deviation of three replicates. Columns with different letters are statistically different at $p < 0.05$ according to the ANOVA Newman–Keuls post hoc test.

The graph in Figure 8 shows that almond skin extract exhibits inhibition of α-amylase activity. The results ranged from 30% to 70% for almond skin extract ($IC_{50} = 27.87\ \mu g/mL$) and 42% to 75% for acarbose ($IC_{50} = 14.24\ \mu g/mL$), which confirms that almond skin extract can modulate α-amylase enzymatic activity. Different types of phenolic compounds have been reported for almond skin extracts, including hydroxybenzoic acids such as protocatechuic acid and p-hydroxybenzoic acid; hydroxycinnamic acids such as chlorogenic acid and trans-p-coumaric acid; flavanones such as eriodictyol, eryodictiol-7-O-glucoside, naringenin, and naringenin-7-O-glucoside; and flavonols such as kaempferol-3-O-rutinoside, kaempferol-3-O-glucoside, isorhamnetin-3-O-glucoside, quercetin, kaempferol, isorhamnetin, quercetin-

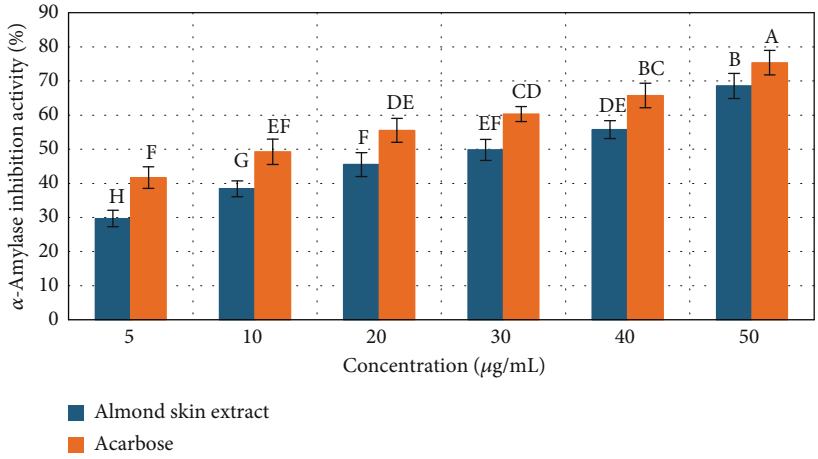

FIGURE 8: Antihyperglycemic activity of almond skin extract compared to acarbose. Each column and bar represent, respectively, the mean and standard deviation of three replicates. Columns with different letters are statistically different at $p < 0.05$ according to the ANOVA Newman–Keuls post hoc test.

3-O-rutinoside, quercetin-3-O-galactoside, quercetin-3-O-glucoside, and isorhamnetin-3-O-rutinoside [54]. Several of these compounds like kaempferol, catechin, epicatechin, and quercetin have been reported by Ali Asgar [55] to inhibit enzymes involved in starch digestion.

4. Conclusion

In conclusion, the valorization and extraction of phenolic compounds from almond skin offer significant potential for enhancing both nutritional value and industrial applications. The ultimate goal of this study is to optimize RSM and ANN extraction using microwaves to maximize the yield and bioactivity of the phenolic extracts. The optimal conditions for phenolic extraction from almond skin with RSM were 661 W, 91 s, and 51% ethanol, and with ANNs, they were 562 W, 30 s, and 52% ethanol.

The results of ANNs and RSM models based on validation data showed that RSM ($R^2 = 0.97$) and ANNs ($R^2 = 0.99$) are useful and perfect methods to predict TPC by applying the MAE process; however, ANNs have higher accuracy. The almond skin extract demonstrated significant AA, as shown by DPPH radical scavenging (IC_{50} = 5.39 ± 0.35 μg/mL), phosphomolybdate ammonium assay, OH• scavenging (IC_{50}042002mg/mL), and ferrous ion chelation. In in vitro test for antihyperglycemic activity, the extract strongly inhibited α-amylase with an IC_{50} of 27.87 μg/mL, approaching the IC_{50} of the therapeutic drug acarbose (14.24 μg/mL). Therefore, almond skin serves as a natural source of bioactive phenolic compounds and offers numerous prospects for value-adding in a variety of industries, such as food, cosmetics, and medicines.

The research findings for MAE optimization with RSM and ANN models will provide effective guidelines, and the results would be a good database of the food industry applications for use in healthcare food.

Data Availability Statement

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare no conflicts of interest.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. *(Supporting Information)*

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